Trypanosomiasis

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Trypanosomes

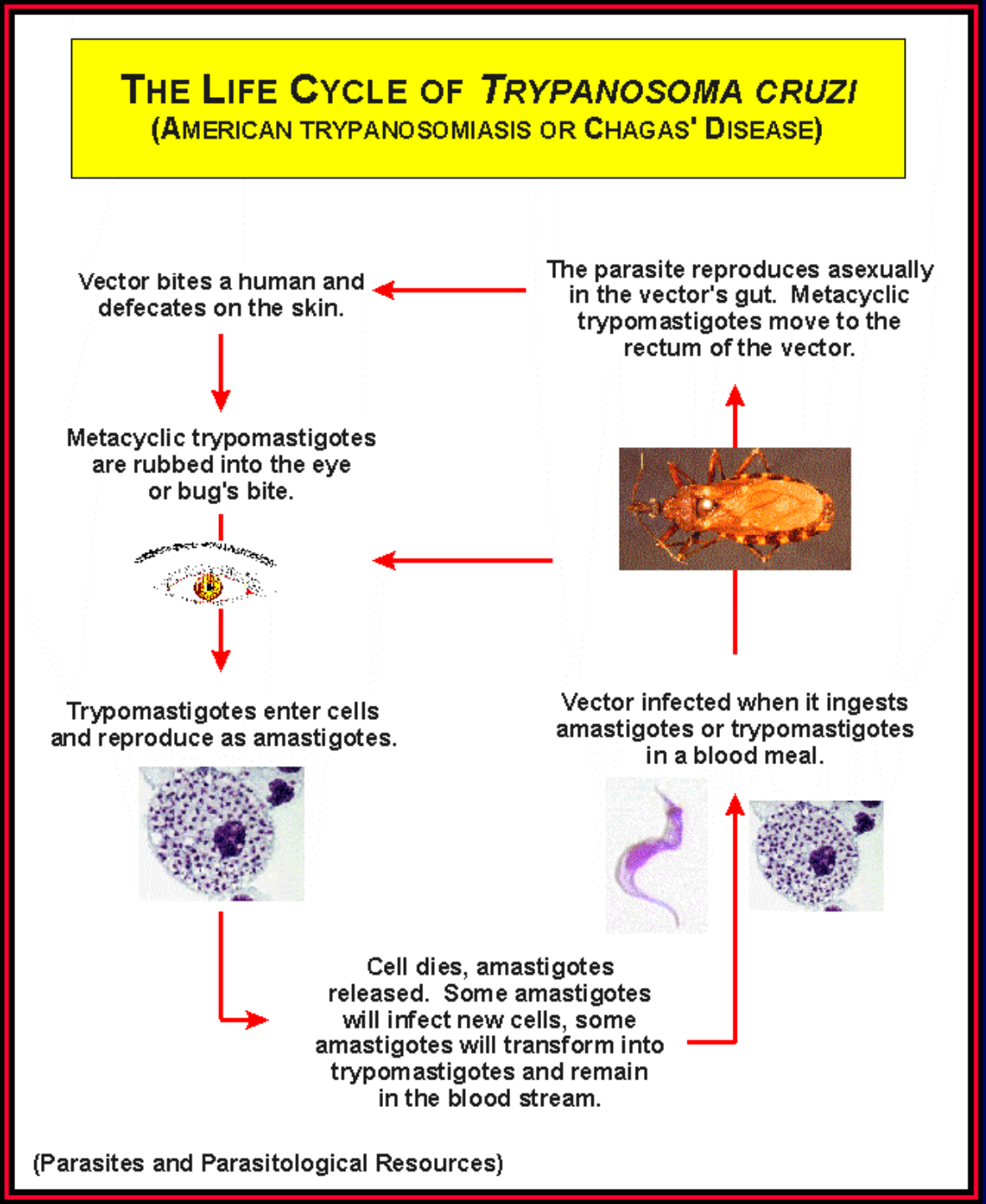
- Genus Trypanosoma
- 20 species
  - 3 pathogenic to humans
  - Others may affect domestic animals
- Flagellated protozoa

Trypaonsomes

- American = Chagas' disease
  - *T. cruzi*
- African = Sleeping Sickness
  - *T. brucei rhodesiense*
  - *T. brucei gambiense*
- Non-pathogenic
  - *T. brucei brucei* among many others

American Trypanosomiasis

- Epidemiology
  - Southern U.S to South America
  - Most cases from Brazil
  - Highest seroprevalence: rural Bolivia (20%)
  - Seropositive much higher than clinical disease
  - Classically disease of rural poor, but changing
    - Migration to cities
    - Control programs aimed at rural areas


THE LIFE CYCLE OF TRYPANOSOMA CRUZI
(AMERICAN TRYPANOSOMIASIS OR CHAGAS' DISEASE)
Vector bites a human and defecates on the skin.
The parasite reproduces asexually in the vector's gut. Metacyclic trypomastigotes move to the rectum of the vector.
Metacyclic trypomastigotes are rubbed into the eye or bug's bite.
Trypomastigotes enter cells and reproduce as amastigotes.
Vector infected when it ingests amastigotes or trypomastigotes in a blood meal.
Cell dies, amastigotes released. Some amastigotes will infect new cells, some amastigotes will transform into trypomastigotes and remain in the blood stream.
(Parasites and Parasitological Resources)

American Trypanosomiasis

www.biosci.ohio-state.edu/.../chagas_lifecycle.gif

American Trypanosomiasis

- Reservoir
  - Many mammals, especially domestic animals
  - Dogs implicated b/c close to family and sleep indoors
- Vector = triatomines or reduvid bugs
  - “Kissing beetles”, prefer human blood
- Other transmission less likely
  - Transfusions, congenital, ingestion, occupational

American Trypanosomiasis

- Acute Illness
  - Pathology
    - Rapid parasite multiplication in cyst
    - Rupture leads to release of amastigotes
    - Amastigotes found in all organs, but primarily:
      - Brain, liver, heart, GI tract

American Trypanosomiasis

- Acute Illness
  - 7-14 days incubation period
  - Lasts 4-8 weeks
  - Asymptomatic: majority
  - Mild, febrile syndrome: 10-20%
  - Severe illness: <5%
    - Acute heart failure, EKG changes, myocarditis, blocks
    - Meningoencephalitis
    - More common in young

American Trypanosomiasis

- Acute Illness
  - Fever
    - High, continuous in severe disease
    - Lower in less severe cases
  - Elastic, nonpitting edema (face and body)
  - Hepatosplenomegaly, lymphadenopathy
  - Anemia, lymphocytosis
  - Mildly elevated LFT’s

American Trypanosomiasis

- Acute Illness
  - Inoculation granuloma: 50%
    - “chagoma”
    - Small papule that enlarges over 7-10 days
  - Conjunctival irritation
    - “Romana’s sign”
      - Bipalpebral, unilateral, chronic edema

American Trypanosomiasis

- Indeterminate Phase
  - Asymptomatic
  - *T. cruzi* antigen positive, low-level parasitemia
  - 10-30% display chronic Chagas disease decades later

American Trypanosomiasis

- Chronic Disease
  - Cardiomyopathy
    - Insidious, presents 20-30 years after inoculation
    - Symptomatic AV block, CHF, SCD, emboli
  - Megasyndromes
    - Megaesophagus
      - Progressive swallowing difficulty
    - Megacolon
      - Progressive constipation, distention

American Trypanosomiasis

- Diagnosis
  - Parasitologic: Parasites in blood or tissue
    - Wet preps or Giemsa stains of blood while febrile
    - CSF, pericardial fluid, masses, BM, organ biopsies
    - Xenodiagnosis: let bugs feed and look at their feces
    - In vitro culture with biphasic media
    - Animal inoculation: takes 5-15 days
  - Use parasitologic tests for acute illness, congenital infection, transfusion illness, lab worker

American Trypanosomiasis

- Diagnosis
  - Serologic: antibodies to *T. cruzi*
    - Persist for life
    - Presumptive diagnosis for chronic infection
    - Many cross reactions: leisch, syphilis, malaria, CVD
    - US: 3 ELISA bases tests
  - Best for indeterminate or chronic disease

American Trypanosomiasis

- Treatment
  - Nifurtimox
    - Nitrofuran not licensed in U.S.
    - Available for domestic use in via IND protocol
    - Active against trypomastigotes and amastigotes
    - Inhibits pyruvic acid synthesis: affects CHO metab
    - Big Risks: lymphomas (rabbits), polyneuropathy (usually resolves after treatment)
    - Side Effects: tremor, excitation, insomnia, anorexia, weight loss, peripheral neuritis, psychosis, hemolytic anemia with G6PD deficiency

American Trypanosomiasis

- Treatment
  - Benznidazole
    - Nitroimidazole derivative not available in U.S.
    - Works against trypomastigotes and amastigotes
    - 50% photosensitivity rashes
    - Other SE's: peripheral neuritis, anorexia, weight loss, cytopenias
    - Children tolerate better than adults

American Trypanosomiasis

- Other Treatments
  - Studied, may be useful, no recommendations:
    - Allopurinol, Itraconazole
  - Immune-modulators
    - INF-gamma – used in combination with nifurtimox or benznidazole reported
    - Potentially useful for immune compromised patients

American Trypanosomiasis

- Nifurtimox
  - Adults: 8-10 mg/kg/day divided q8, after meals
  - Children: 15mg/kg/day divided q8, after meals
  - Course varies: 30 to 120 days
- Benznidazole
  - All: 5-10mg/kg daily divided q12
  - 30-60 day course
- Who to treat:
  - Acute: definitely, Indeterminate: controversial
  - Chronic: usually supportive and do not use Rx

American Trypanosomiasis

- Supportive Therapy
  - Cardiac
    - Antiarrhythmics, but NOT beta-blockers
    - Pacers if walls aren't too thin
    - Thromboembolic prophylaxis
    - Transplantation: not recommended as dz recurs
  - Megasyndromes
    - Balloon dilation of LES, Heller's procedure, total esophagectomy with intestinal replacement, botox
    - Dietary fiber + stool softeners, regular use of laxatives/enemas, resection for severe cases

American Trypanosomiasis

- Outcomes
  - <5% mortality in acute phase
  - 70-90% exposed never develop chronic disease
  - 25% eventually have EKG abnormalities
  - 1% megasyndromes at 20-50 years old
  - Predictors of death:
    - <50% 4 year survival if: CHF, global LV dysfct, apical LV aneurysm at presentation

American Trypanosomiasis

- Disease Control
  - Bug spray on walls
  - Brick rather than “thatched-roofed” or mud huts
  - Cultural teaching
  - Night-lights (bugs prefer dark)
  - Banning animals from house
  - National and multinational programs
  - Screening blood donor pool or at least treating blood with gentian violet to kill organisms if not possible
  - Congenital: mothers avoid nursing until treated

African Trypanosomiasis

	Gambian	Rhodesian
Agent	***T. b. gambiense***	***T. b. rhodesiense***
Vector	**Riverine Tsetse (*G. palpalis* gp.)**	**Savanna Tsetse (*G. morsitans*)**
Distribution	**West and Central Africa**	**Eastern and Southern Africa**
High-Incidence Countries	**The Congo, Angola, Sudan, Uganda, Congo-Brazaville**	**Uganda, Tanzania, Mozambique, Zambia**

African Trypanosomiasis. Hunter's Tropical Medicine. WB Saunders Company, 2000; 644

African Trypanosomiasis

	Gambian	Rhodesian
Location	**Rivers, watering holes**	**Cleared bush, savannas**
Reservoir	**Humans**	**Antelope, cattle**
Disease	**Chronic**	**Acute**
CNS Invasion	**Late**	**Early**
Duration	**Months to years**	**Weeks to months**

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African Trypanosomiasis

	Gambian	Rhodesian
Parasitemia	**Low**	**High**
Diagnosis	**Aspirate lymph node, CSF examination**	**Peripheral blood or CSR examination**
Serology	**Card Agglutination Test for Tryp.**	**None**
Control	**Active case finding**	**Tsetse trapping**

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African Trypanosomiasis

- Treatment
  - *T. b. rhodesiense* is more resistant of two
  - Distinguish primarily by geographic location
  - CNS disease warrants different therapy
    - LP must be performed on all patients, even in absence of symptoms
    - CNS disease defined as: evidence of trypanosomes or pleocytosis >5 cells/mm^3

African Trypanosomiasis

- Non-CNS Treatment: *T. b. gambiense*
  - Pentamidine
    - Aromatic diamidine approved in US but not for this
    - 4mg/kg daily X 7 days IV or IM = 93% cure rates
    - Adverse events: sterile abscesses at injection site, hypocalcemia, hyperkalemia, renal failure, neutropenia, arrhythmias, hypoglycemia, post-therapy diabetes
    - 1% die on therapy for unclear reasons
    - Suramin less effective; melarsoprol too toxic

African Trypanosomiasis

- CNS Treatment: *T. b. gambiense*
  - Eflornithine
    - inhibits ornithine decarboxylase
  - Equal to melarsoprol and less toxic
  - Expense is limiting factor for use, huge volumes another
  - 100mg/kg IV q6 X 14 days
    - 90% cure of late disease, 98% cure of relapses
    - 2% die on therapy
  - SE's: cytopenias from BM toxicity in >50%

African Trypanosomiasis

- Melarsoprol
  - Toxic, but cheap, and commonly used
  - Trivalent arsenical with 94-97% cure rates
  - 4-6% death rate
  - <1% penetrates CSF, but works b/c so effective
  - No evidence of resistance despite years of use
  - 3.6mg/kg (max 180 mg) IV daily X 3, repeat in 1 week, again in 2 weeks if CSF cell counts >20.
  - SE's: Reactive encephalopathy serious in 4-8%, polyneuropathy (10%)

African Trypanosomiasis

- Non-CNS Treatment: *T. b. rhodesiense*
  - Suramin considered better than pentamidine
  - Failure rate variable: 0-31%
  - 200mg test dose recommended b/c of uncommon anaphylaxis at 1/20,000
  - 20mg/kg IV (max 1.5g) days 1, 3, 6, 14, 21
  - SE's: fever, proteinuria, paresthesias, urticaria
  - Poor CSF penetration precludes CNS use

African Trypanosomiasis

- CNS Treatment: *T. b. rhodesiense*
  - Melarsoprol cures 95%
  - Encephalopathy occurs in 5-18%; Mortality in 3-12% on therapy
    - Both higher than with T. b. gambiense
  - Complicated incremental WHO dosing schedule where small doses are increased gradually – no comparative trials